Drug Class Review

HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin

Final Report Update 5
Executive Summary

November 2009

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

Update 4: August 2006
Update 3: September 2005
Update 2: March 2004
Update 1: July 2003
Original Report: April 2002
The literature on this topic is scanned periodically.

Authors for Update 5:
M.E. Beth Smith, DO
Nancy J. Lee, PharmD, BCPS
Elizabeth Haney, MD
Susan Carson, MPH

Original authors:
Mark Helfand, MD, MPH
Cathy Kelley, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

INTRODUCTION

In the United States, coronary heart disease and cardiovascular disease account for nearly 40% of all deaths each year. Coronary heart disease continues to be the leading cause of mortality and a significant cause of morbidity among North Americans. In 2006, coronary heart disease claimed 607 000 lives, translating into about 1 out of every 5 deaths in the United States. High levels of cholesterol, or hypercholesterolemia, are an important risk factor for coronary heart disease. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum low-density lipoprotein cholesterol concentrations. They are first-line agents for patients who require drug therapy to reduce serum low-density lipoprotein cholesterol concentrations.

Six statins are available in the United States and Canada (Table 1).

Table 1. Included statins

Statin	Strength	Dose range	Usual starting dose
Atorvastatin (Lipitor®)	10 mg, 20 mg, 40 mg, 80mg	10-80 mg once daily	20 mg
Fluvastatin (Lescol and Lescol XL®)	20 mg, 40 mg XL, 80 mg	20-80 mg once daily or divided bid; XL once daily	20 mg
Lovastatin[a] (Mevacor and extended release Altoprev®)	20 mg, 40 mg, 20 mg, 40 mg, 60 mg	20-80 mg daily or divided bid 20-80 mg once daily Altoprev	20 mg
Pravastatin[a] (Pravachol®)	10 mg, 20 mg, 40 mg, 80 mg (also 30 mg in generic only)	10-80 mg once daily	40 mg
Rosuvastatin (Crestor®)	5 mg, 10 mg, 20 mg, 40 mg	5-40 mg once daily	10 mg
Simvastatin[a] (Zocor®)	5 mg, 10 mg, 20 mg, 40 mg, 80 mg	5-80 mg once daily	40 mg

[a] Available in generic and trade form.

Three fixed-dose combination products containing a statin and another lipid-lowering drug are available in the United States while only 1 is currently available in Canada (Table 2).

Table 2. Included fixed-dose combination products

Fixed-dose combination product	Strength	Dose range	Usual starting dose
Lovastatin/Niacin-ER (Advicor®)	20/500 mg 20/750 mg 20/1000 mg 40/1000 mg	20/500 mg – 80/2000 mg once daily	20/500 mg
Simvastatin/Niacin-ER (Simcor®), not available in Canada	20/500 mg 20/750 mg 20/1000 mg	10/500 – 40/2000 mg	20/500 mg if niacin naive
Simvastatin/Ezetimibe (Vytorin®), not available in Canada	10/10 mg 10/20 mg 10/40 mg 10/80 mg	10/10 – 10/80 mg	10/20 mg (10/40 if need >55% LDL reduction)

Scope and Key Questions

The purpose of this review is to compare the efficacy and adverse effects of different statins. Since the last review, the participating organizations have decided to include pediatric population and fixed-dose combination products containing a statin and another lipid-lowering drug. The participating organizations approved the following key questions to guide this review:

1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?
    a. Are their doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent reduction in low-density lipoprotein cholesterol between statins?
    b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid-lowering drug to achieve National Cholesterol Education Panel goals?

2. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to raise high-density lipoprotein cholesterol?
    a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent increase in high-density lipoprotein cholesterol between statins?
    b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid-lowering drug to achieve National Cholesterol Education Panel goals?

3. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?

4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid-lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?

5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in the general population of children or adults?

6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in special populations or with other medications (drug-drug interactions)? In addressing this question, we will focus on the following populations:
    a. Patients with HIV
    b. Organ transplant recipients
    c. Patients at high risk for myotoxicity (e.g., patients with a history of statin-associated muscle-related harms due to drug-drug/drug-food interactions, patients co-administered fibrates, patients taking potent 3A4 inhibitors, elderly patients, especially elderly females)
    d. Patients at high risk for hepatotoxicity
    e. Patients using fibrates (gemfibrozil, fenofibrate, fenofibric acid) or niacin
    f. Children with nephrotic syndrome

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Central Register of Controlled Trials (2nd Quarter 2009), MEDLINE (1966-June 4, 2009), PreMEDLINE (through June 4, 2009), and reference lists of review articles. Pharmaceutical manufacturers were invited to submit dossiers and citations. For Update 5 we received dossiers from the manufacturers of fluvastatin, rosuvastatin, and the fixed-dose combination products simvastatin/niacin extended release and simvastatin/ezetimibe.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria. These criteria are based on those developed by the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK). For Key Question 3, we rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in 1 or more categories were rated poor quality; trials meeting all criteria were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are

likely to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population and how similar patients were to the target population in whom the intervention will be applied.

RESULTS

Overview

Update searches identified 3089 citations. We retrieved 338 potentially relevant articles for review. Of these, 74 randomized controlled trials and 61 additional publications (other study designs) were included.

Summary of Findings

Key Question 1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?

Adults

For adult patients who require low-density lipoprotein cholesterol reductions of up to 35% to meet their goal, any of the statins are effective. In adult patients requiring a low-density lipoprotein cholesterol reduction of 35% to 50% to meet the National Cholesterol Education Program goal, atorvastatin 20 mg or more, lovastatin 80 mg, rosuvastatin 10 mg or more, simvastatin 20 mg or more, ezetimibe-simvastatin fixed-dose combination product 10/10 mg or more, and niacin extended release-lovastatin fixed-dose combination product 1000/40 mg or 2000/40 mg daily are likely to meet the goal. The niacin extended-release lovastatin fixed-dose combination product 1000/40 mg and 2000/40 mg has greater adverse events and a higher number of patients who discontinue therapy due to adverse events.

Among high-potency and high-dose statins, atorvastatin 40 mg or 80 mg daily and rosuvastatin 20 mg or more reduced low-density lipoprotein cholesterol by 50% or more; atorvastatin 80 mg had a higher rate of some adverse effects (gastrointestinal disturbances and transaminase elevation) than simvastatin 80 mg daily in a trial in which the low-density lipoprotein lowering of atorvastatin was greater than that of simvastatin; and adverse event rates in patients using rosuvastatin 40 mg were similar to rates in patients using atorvastatin 80 mg in short-term trials.

In adult patients requiring a low-density lipoprotein cholesterol reduction of greater than 50%, the higher doses of ezetimibe-simvastatin at 10/40 mg and 10/80 mg were more likely to meet the National Cholesterol Education Program Adult Treatment Panel III goal than an equivalent high potency statin.

Children

Trials of statins in children have been conducted primarily in children with heterozygous or homozygous familial hypercholesterolemia, or other familial dyslipidemias and eight trials of various statins showed improvement in low-density lipoprotein compared with placebo.

In meta-analysis, statins reduced low-density lipoprotein cholesterol in children taking a statin by 32% (95% CI, 37 to 26). One trial compared ezetimibe/simvastatin to simvastatin alone and demonstrated a 54% reduction in low-density lipoprotein cholesterol for combination compared to 38% reduction for simvastatin alone.

Key Question 2. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to increase high-density lipoprotein cholesterol?

Adults

When statins were provided in doses that reduced low-density lipoprotein cholesterol by equivalent amounts, a similar percent increase in high-density lipoprotein cholesterol could be achieved. There was conflicting evidence about simvastatin compared with atorvastatin, with some studies finding no difference and others finding simvastatin superior, and some studies found greater increases in high-density lipoprotein cholesterol with low-dose rosuvastatin compared with atorvastatin, while other studies found no difference.

Amongst the high potency statins, high dose of rosuvastatin increased high-density lipoprotein cholesterol more than high dose simvastatin or atorvastatin. Ezetimibe-simvastatin fixed-dose combination had an equivalent effect on increasing high-density lipoprotein cholesterol as simvastatin alone, however ezetimibe-simvastatin was not as effective as fenofibrate or niacin in increasing high-density lipoprotein cholesterol.

Fixed-dose combination products containing extended-release niacin with lovastatin or simvastatin were more effective in increasing high-density lipoprotein cholesterol than simvastatin 20-40 mg, but with more adverse events.

Children

Statins decreased high-density lipoprotein cholesterol in 1 study of atorvastatin and did not change high-density lipoprotein cholesterol in 5 other trials of statins including rosuvastatin, simvastatin, lovastatin, and pravastatin. Overall, the pooled result indicated that statins increased high-density lipoprotein cholesterol by 3% (95% CI, 0.6 to 5.6).

Key Question 3. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?

Adults

Information from head-to-head trials of adults was limited. In adult patients with no known coronary heart disease, there were still no head-to-head trials of statins or fixed-dose

combination products containing a statin (and another lipid-lowering drug). In adult patients with known coronary heart disease, those who had a recent myocardial infarction found high dose atorvastatin 80 mg daily reduced cardiovascular events compared with pravastatin 40 mg daily (PROVE-IT). For every 25 patients treated with atorvastatin 80 mg instead of pravastatin 40 mg, 1 coronary event was prevented. In patients who had a *history* of myocardial infarction (IDEAL), high-dose atorvastatin (80 mg) and simvastatin (20 mg) did not differ in the primary endpoint (coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation). More high-dose atorvastatin patients discontinued due to adverse events (9.6% compared with 4.2%; $P<0.001$), and there were more cases of elevated liver enzymes and myalgia with high-dose atorvastatin. No studies of fixed-dose combination products in this population were found.

The amount of information on cardiovascular outcomes available from placebo-controlled trials for each statin differed substantially and there were no studies of fixed-dose combination products that reported cardiovascular outcomes.

In adult patients with no known coronary disease (primary prevention), pravastatin reduced all-cause mortality and cardiovascular events over 4.9 years in 1 trial, lovastatin reduced cardiovascular events over 5.2 years in 1 trial, and rosuvastatin reduced all-cause mortality and cardiovascular events over median of 1.9 years in 1 trial.

In patients with mixed populations or subjects with coronary risk equivalents, simvastatin reduced all-cause mortality and cardiovascular events, atorvastatin and fluvastatin reduced cardiovascular events, and pravastatin reduced all-cause mortality and cardiovascular events in Japanese adults.

In patients with known coronary heart disease (secondary prevention), atorvastatin reduced cardiovascular events, simvastatin reduced all-cause mortality and cardiovascular events, pravastatin reduced all-cause mortality and cardiovascular events, and fluvastatin reduced coronary events when started after percutaneous coronary intervention. Studies of angiographic progression of atherosclerotic plaques provided fair-quality but indirect evidence that lovastatin is effective in preventing cardiovascular events in patients with coronary heart disease. This finding is weakened because of possible reporting bias. There are still no completed studies of rosuvastatin with coronary heart disease endpoints in patients with coronary disease.

Children

Studies of statins in children have not been conducted with long enough follow-up to assess for outcomes related to cardiovascular mortality and morbidity.

Key Question 4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid-lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?

Adults

There was good evidence from randomized trials that women and the elderly benefit from statin therapy, however data about efficacy and safety in African-Americans, Hispanics, and other ethnic groups were weaker and there was no evidence that one statin is safer than another in these groups. A pharmacokinetic study conducted in the United States demonstrated a 2-fold higher blood level of rosuvastatin in Asian subjects (having either Filipino, Chinese, Japanese,

Korean, Vietnamese, or Asian-Indian origin) compared with a White control group taking the same dose. The rosuvastatin label has been revised to note that this increase should be considered when making rosuvastatin dosing decisions for Asian patients.

Children

No trials have evaluated statins in children with diabetes or obesity. One study demonstrated 21% reduction in low-density lipoprotein with simvastatin in children with neurofibromatosis 1.

Key Question 5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in the general population of children or adults?

Adults

There was insufficient evidence to determine which statin or statins are safer with regard to muscle and liver toxicity in adults. Four studies evaluating the benefit of atorvastatin 80 mg daily in reducing coronary heart disease on health outcomes observed a significantly higher rate of substantial elevations in liver transaminases in the atorvastatin groups in comparison with angioplasty, usual care, placebo, or pravastatin 40 mg. The clinical significance of asymptomatic liver enzyme elevations from statins has been questioned, however.

Niacin extended release fixed-dose combination products caused increased adverse events leading to discontinuation of therapy compared with statin monotherapy.

Children

Adverse events were variably reported; methods of detection and assessment of adverse events were often not specified. Multiple studies reported no significant elevations in both creatine kinase and aspartate aminotransferase/alanine aminotransferase over the course of the study. Elevations in aspartate aminotransferase/alanine aminotransferase occurred but were either lower than 3 times the upper limit of normal, or resolved with interruption/discontinuation of medication. Elevations in creatine kinase occurred with simvastatin and simvastatin plus ezetimibe, and all returned to normal with cessation of medication.

Key question 6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in special populations or with other medications (drug-drug interactions)?

Adults

Studies that included adult patients with diabetes did not have higher rates of adverse events than other studies. In general, statin-fibrate combination increased risk of musculoskeletal-related adverse events compared with statin monotherapy and it appeared that the risk was greater with statin-gemfibrozil combination than with statin-fenofibrate combinations.

Children

One study of fluvastatin in children with minimal change glomerulonephritis demonstrated decrease in total cholesterol and reported no side effects.

SUMMARY

Table 3 summarizes the level and direction of evidence for each key question.

Table 3. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
ADULTS		
1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?	Fair	The ideal study would be a double-blind, intention-to-treat randomized trial in which equipotent doses of different statins were compared with regard to low-density lipoprotein-lowering, withdrawals, and adverse effects. No studies met these stringent criteria.
a. Are their doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent reduction in low-density lipoprotein cholesterol between statins?	Fair-to-good	Results of a large number of trials are generally consistent with information from the manufacturer. When statins are provided in doses that are approximately equipotent, a similar percent reduction in low-density lipoprotein cholesterol can be achieved. In active-control trials, the fixed-dose combination of ezetimibe-simvastatin had a significant increase in low-density lipoprotein cholesterol lowering compared to statin monotherapy.
b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid-lowering drug to achieve National Cholesterol Education Panel goals?	Good for most comparisons (see text)	For patients who require low-density lipoprotein cholesterol reductions of up to 35% to meet their goal, any of the statins are effective. In patients requiring a low-density lipoprotein cholesterol reduction of 35% to 50% to meet the National Cholesterol Education Program goal, atorvastatin 20 mg or more, lovastatin 80 mg, rosuvastatin 10 mg or more, and simvastatin 40 mg or more daily are likely to meet the goal. Atorvastatin 80 mg daily and rosuvastatin 20 mg or more can reduce low-density lipoprotein cholesterol by 50% or more. Based on fair-quality studies, atorvastatin 80 mg daily resulted in 5 to 6 additional percentage points of low-density lipoprotein reduction than simvastatin 80 mg (53% to 54% vs. 47% to 48%), but had significantly higher rates of some adverse events. In head-to-head studies rosuvastatin 40 mg had greater reduction in low-density lipoprotein cholesterol than atorvastatin 80 mg with similar frequency of adverse events. In patients requiring a low-density lipoprotein cholesterol reduction of greater than 50%, the higher doses of ezetimibe-simvastatin at 10/40 mg and 10/80 mg are more likely to meet the National Cholesterol Education Program Adult Treatment Panel III goal than an equivalent high potency statin.
2. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to raise	Fair-to-good	When statins are provided in doses that are approximately equipotent for lowering LDL-C, a similar percent increase in high-density lipoprotein cholesterol can be achieved. There is conflicting evidence about simvastatin vs. atorvastatin,

Key question	Strength of evidence	Conclusion
high-density lipoprotein cholesterol?		with some studies finding no difference and others finding simvastatin superior. Some studies found greater increases in high-density lipoprotein cholesterol with rosuvastatin compared with atorvastatin, while other studies found no difference.
3. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?	NA	There are no controlled trials comparing equivalent doses of 2 or more statins to reduce the risk of coronary events, stroke, or death.
Which statins have been shown to reduce all-cause mortality?	Good	Patients who have never had CHD: pravastatin (high-risk patients), simvastatin (mixed populations); rosuvastatin (patients with elevated C-reactive protein) Patients with CHD: atorvastatin (post-MI), pravastatin, simvastatin
Which statins have been shown to reduce cardiovascular mortality?	Good	Patients who have never had CHD: Pravastatin, simvastatin Patients with CHD: simvastatin, atorvastatin
Which statins have been shown to reduce CHD events?	Fair-to-good	Patients who have never had CHD: atorvastatin (high-risk patients, patients with diabetes), lovastatin (average-risk patients), pravastatin (high-risk patients), simvastatin (mixed populations) ; rosuvastatin (patients with elevated C-reactive protein) Patients with CHD: atorvastatin, simvastatin, pravastatin. Patients after PTCA: fluvastatin, pravastatin.
Which statins have been shown to reduce strokes?	Good	Atorvastatin, pravastatin, simvastatin, rosuvastatin (patients with elevated C-reactive protein)
Patients with diabetes	Good	There are good efficacy data for people with diabetes. Atorva 10 mg reduced cardiovascular events in a primary prevention trial of patients with diabetes (CARDS), and simvastatin 40 mg reduced cardiovascular events in patients with diabetes (Heart Protection Study). In a subgroup analysis of the LIPS trial, there was a reduction in coronary events (cardiac death, nonfatal MI, CABG, or repeat PCI) with fluvastatin 80 mg in patients with diabetes who had undergone successful PCI. Studies that included people with diabetes had rates of adverse effects similar to other studies.

Key question	Strength of evidence	Conclusion
4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid-lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?	Good (elderly, women)-to-Fair to Poor (African Americans, Hispanics, and other ethnic groups)	The benefits of statins have been documented in women and the elderly. There are almost no data about African Americans, Hispanics, or other ethnic groups. In short-term head-to-head trials, reductions in LDL-C and frequency of adverse events with rosuvastatin 10 to 20 mg and atorvastatin 10 to 20 mg in Hispanic, South Asian, and African American patients were similar to those observed in studies conducted in primarily white non-Hispanic populations.
Are there differences in safety of statins in different demographic groups (age, sex, race)?	Poor	There are no data from clinical trials comparing the safety of different statins in women, the elderly, or African Americans. A pharmacokinetic study of rosuvastatin conducted in the United States demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian origin) compared with a Caucasian control group.
5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in the general population of children or adults?	Good for statins monotherapy Fair to poor for fixed dose combination products	Although creatine kinase elevations are common, the risk of symptomatic myopathy is low. All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, rosuvastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia, and myopathy to rhabdomyolysis. Two meta-analyses of clinical trials found rates of elevated transaminases (liver function tests) to be no higher among patients taking statins than among those receiving placebo. There is no evidence that elevated transaminases associated with statin use increase the risk of clinically significant liver failure. In a trial of 2 doses of atorvastatin, the incidence of persistent elevations in liver aminotransferase levels 2 per 1000 in patients taking atorvastatin 10 mg daily, vs. 1.2 per 1000 in patients taking 80 mg daily. There is insufficient evidence to determine which statin or statins are safer with regard to muscle toxicity or elevated liver enzymes. Among high potency statins, at doses below 80 mg, rates of adverse events and withdrawals due to adverse events were similar in patients taking atorvastatin or simvastatin. Atorvastatin 80 mg had a higher rate of some adverse effects (gastrointestinal disturbances and transaminase elevation) than simvastatin 80 mg daily in a trial in which the low-density lipoprotein lowering of atorvastatin was greater than that of simvastatin. Adverse event rates in patients using rosuvastatin 40 mg were similar to rates in patients using atorvastatin 80 mg in short-term trials. We identified very little evidence of harms in the trials of the fixed dose combination product trials. The majority of trials were not longer than 12 weeks in duration.
6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when		

Key question	Strength of evidence	Conclusion
used in special populations or with other medications (drug-drug interactions)?		
Special populations: Patients with diabetes	Good	Studies that included people with diabetes had rates of adverse effects similar to other studies.
Drug interactions	Fair	The combination of any statin with fibrates, and to a lesser extent niacin, can result in a higher risk for myopathy or rhabdomyolysis.
CHILDREN		
1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?	Fair-to-poor	In one head-to-head trial conducted in adults and children with homozygous familial hypercholesterolemia, atorvastatin 80 mg and rosuvastatin 80 mg were similarly efficacious for reducing low-density lipoprotein cholesterol (18% for atorvastatin, 19% for rosuvastatin). In placebo-controlled trials of atorvastatin, lovastatin, pravastatin, and simvastatin, statins reduced low-density lipoprotein cholesterol in children with familial hypercholesterolemia by 32% (95% CI, 37 to 26). In one trial, the fixed dose combination product simvastatin/ezetimibe reduced low-density lipoprotein more than simvastatin alone (54% vs. 38%). There were no trials of fluvastatin or the fixed dose combination products lovastatin/niacin extended-release or simvastatin/niacin extended-release in children.
2. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to raise high-density lipoprotein cholesterol?	Fair-to-poor	In one head-to-head trial of atorvastatin 80 mg vs. rosuvastatin 80 mg conducted in adults and children with homozygous familial hypercholesterolemia, there was no difference in high-density lipoprotein cholesterol levels after 6 weeks. In placebo-controlled trials of atorvastatin, lovastatin, pravastatin, and simvastatin, statins increased high-density lipoprotein cholesterol in children with familial hypercholesterolemia by 3% (95% CI, 0.6 to 5.6). One trial of the fixed dose combination product simvastatin/ezetimibe compared with simvastatin alone showed no change in high-density lipoprotein levels. There were no trials of fluvastatin or the fixed dose combination products lovastatin/niacin extended-release or simvastatin/niacin extended-release in children.
3. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause	Poor	No evidence in children.

Key question	Strength of evidence	Conclusion
mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?		
4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid-lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?	Poor	No evidence in children with diabetes or obesity. One placebo-controlled trial in children with neurofibromatosis 1 showed reduction in low-density lipoprotein levels with simvastatin, but no change in high-density lipoprotein levels.
5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in the general population of children or adults?	Fair-to-poor	Multiple studies reported no significant elevations in creatine kinase and AST/ALT. If AST/ALT elevations occurred, they were either lower than 3 times the upper limit of normal, or resolved with discontinuation of medication. In trials, reporting of adverse events was poor.
6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in special populations or with other medications (drug-drug interactions)?	Poor	No comparative evidence in children.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CABG, coronary artery bypass graft; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.